AR 201-12549 b25

ROBUST SUMMARY
ALKYL SULFIDE CATETGORY
CAS # 68515-88-8
HEALTH ELEMENTS: REPEATED DOSE TOXICITY

Test Substance	
CAS #	CAS# 68515-88-8
Chemical Name	Pentene, 2,4,4-trimethyl-, sulfurized
Remarks	97% purity This chemical is also referred to as trimethyl pentene derivative in the HERTG's Test Plan for Alkyl Sulfide Category. For more information on the chemical, see Section 2.0 "Chemical Description of Alkyl Sulfide Category" in HERTG's Test Plan for Alkyl Sulfide Category.
Method	
Method/Guideline followed	OECD 412
Test Type	4-week inhalation toxicity study in rats
GLP (Y/N)	Y
Year (Study Performed)	1989
Species	Rat
Strain	Sprague-Dawley CD, 7 weeks old at initiation of treatment
Route of administration	Aerosol inhalation
Duration of test	4 weeks of treatment for all doses, and a 3 week recovery period in the control and high dose satellite recovery groups
Doses/concentration levels	0, 15, 50 and 150 mg/m^3
Sex	Males and females
Exposure period	4 weeks of inhalation treatments followed by a 3 week recovery period
Frequency of treatment	Inhalation treatment for 6 hours/day, 5 days/week for 4 weeks at the target concentrations
Control group and treatment	10 rats/sex/group for the low and mid dose levels, 15 male and 20 female rats for the high dose level group. Control rats (15 males and 20 females) received mineral oil only at a level of 150 mg/m^3, while in the exposure chamber.
Post exposure observation period	
Statistical methods	Body weight, food consumption, hematology and clinical chemistry parameters, organ weights and organ/body weight ratios were analyzed. Mean values of all dose groups were compared to control at each time interval. Tests included parametric ANOVA with a Dunnett's *post-hoc* test, non-parametric Kruskal-Wallis and Dunn's rank sum test, Bartlett's test for equal variances, and Student's *t*-test.
Remarks field for test conditions	The rats were exposed on each treatment day for 6 hours to the test material (target concentrations = 15, 50, 150 mg/m3) as a liquid droplet aerosol generated by an air atomizing nozzle apparatus delivered into a plexi-glass chamber. Control rats were exposed to in the same manner as the test-material-exposed group except that mineral oil only was administered. The details of the whole body exposure are consistent with those described in OECD guideline 412. The actual exposure concentrations as measured by gravimetric

	analysis were 15, 50 and 160 mg/m^3. Particle size analyses were performed once/week from the test material chamber using a cascade impactor. Animal observations for toxicological signs and mortality were recorded twice daily, once in the morning and once in the afternoon. Over the course of the study. Individual weights were recorded twice pre-test and then weekly during the exposure and recovery periods, and at termination. At the conclusion of the observation period, the surviving animals were euthanized with carbon dioxide. Animals were fasted prior to sacrifice. Five rats/sex were subjected to post-exposure blood analysis (routine hematology and clinical chemistry parameters) on test day 1 for the control and high dose groups, at termination on 5 rats/sex for all dose groups, and on 5 rats/sex from the control and high dose group after three weeks of recovery. Complete gross post mortem examinations were performed on all animals (nasal passages, trachea, external surface, all orifices, the cranial cavity, the brain and spinal cord, and all viscera). Nine major organs were weighed to obtain organ/body weight calculations, 42 individual organs and/or tissues were preserved, and 10 major organs and/or tissues were examined for histopathology.
Results	
Remarks	No NOAEL was assigned to this study. The mass median aerodynamic diameter for the studies ranged from 1.9 to 2.6 microns with a geometric standard deviation ranging from 1.8 to 2.2. This data indicated that the aerosol was of a respirable size in the rat, with at least 96% of the particles 10 microns or less in diameter. Mortality: One high-dose female had convulsive behavior following the third day of exposure, and was found dead the next morning. The cause of death was unclear. There were no other unscheduled deaths in the study. Physical observations: The animals were unremarkable during the exposure period. Weekly detailed observations included an increased incidence of nasal discharge or dried red material on the facial area among the high-dose animals. However, these findings were not temporally consistent nor were they apparent in the lowest two doses of test material. No significant respiratory sounds were noted. Body weights: Although there were no significant differences seen between control and treated groups, there was a trend toward lower body weight gains during the exposure period of the study at all dose levels in the males and with the two highest dose levels in the females. During the three-week recovery period, the high dose animals did not regain the difference in body weight compared to the controls. Hematology: The only significant difference from control values was increased hemoglobin concentration in the high-dose females sacrificed after 4 weeks of exposure. Clinical chemistry: There were several statistically significant differences from the control values at both the post-exposure and post-recovery time intervals. However, these differences

	did not correlate with dose, with sex, with potential target organs or with sacrifice interval. Terminal organ and body weights: Following 4 weeks of exposure to test material, increases in kidney weights were seen in the males at all three dose levels, and were statistically significant in the higher two levels. This effect was considered to renal effects seen microscopically in males (see below). This difference in weight abated following 3 weeks of recovery. Following 4 weeks of exposure, statistically significant increases were seen in high-dose liver weights and liver/body ratio in both sexes. These differences abated following 3 weeks of recovery. Spleen and adrenal weights increased compared to controls in the high dose groups of both sexes. Post-recovery increases in teste, heart, lung and spleen weights were recorded. These effects were not accompanied by pathologic microscopic findings, and therefore, the biological significance was considered equivocal. A few visible gross changes, such as discolored lungs, were noticed in the sacrificed animals. Microscopically, treatment-related effects were seen in the kidneys in the males in a dose-related profile. Findings included globular casts at the cortico-medulary junction, the cortex and medulla, as well as hyaline droplets in the proximal convoluted tubule cells. These responses were seen in males in all treatment groups following 4 weeks of exposure, and in the high-dose group after 3 weeks of recovery. All other microscopic tissue alterations observed in other organs were considered incidental findings.
Conclusions	No NOAEL was assigned to this study.
Data Quality	Reliable without restriction (Klimisch Code)
References	This robust summary was prepared from an unpublished study by an individual member company of the HERTG (the underlying study contains confidential business information).
Other	Updated: 12-28-99